Association between metabolic syndrome and inflammatory bowel disease: a bidirectional two-sample Mendelian randomized study

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Abstract

Introduction: Epidemiological studies have revealed parallel increases in the incidences of metabolic syndrome (MetS) and inflammatory bowel disease (IBD). Clinical observational studies have shown an association between MetS and a poor prognosis of IBD. However, the causal relationship between MetS and IBD remains unclear. This study used bidirectional two-sample Mendelian randomization to investigate potential causal links between MetS and IBD, including ulcerative colitis (UC) and Crohn's disease (CD).

Material and methods: Genetic associations of MetS and its components with IBD were sourced from public databases of European populations. Inverse variance weighting was conducted, with weighted median, Mendelian randomization–Egger (MR-Egger), and Mendelian randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods used as sensitivity analyses. This process was repeated in the opposite direction.

Results: The inverse variance weighted (IVW) method showed that genetic prediction of MetS may be a potential risk factor for CD (OR = 1.34, 95% CI: 1.009–1.779; p = 0.043). In further estimating the different components of MetS, it was found that waist circumference may increase the risk of CD (OR = 1.33, 95% CI: 1.05–1.684; p = 0.018) and hypertension may increase the risk of UC (OR = 1.61, 95% CI: 1.084–2.39; p = 0.018). Reverse analysis showed that IBD may increase triglyceride levels (OR = 1.019, 95% CI: 1.000–1.038; p = 0.049).

Conclusions: This MR analysis showed a causal relationship between genetically predicted MetS and CD, and genetically predicted hypertension and UC. Therefore, these patients need to be closely monitored clinically for the risk of CD/UC comorbidities. In patients with IBD, close monitoring of MetS-associated cardiovascular risk is required.

Key words: metabolic syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's disease.

Introduction

Inflammatory bowel disease (IBD) is a chronic, immune-mediated inflammatory disease of the intestine. Ulcerative colitis (UC) and Crohn's disease (CD) are the two main types of IBD. The pathogenesis of IBD remains unknown, but it involves complex interactions among genetic, environmental, microbial, and immune factors. The incidence of IBD is increasing globally [1]. Metabolic syndrome (MetS) is a group of complex metabolic disorders that includes obesity, dyslipidemia, hypertension, and insulin resistance; the syndrome has a global incidence of approximately 12–31% [2, 3]. The clinical features of MetS include elevated diastolic or systolic blood pressure, increased fasting blood glucose and triglyceride levels, increased waist circumference, and decreased levels of high-density lipoprotein cholesterol [4].

Epidemiological studies have revealed similar upward trends in the incidences of IBD and MetS in recent decades, suggesting a common environmental link between these two diseases. Both diseases share clinically relevant features, such as an increased risk of cardiovascular disease [5, 6] and increased incidences of non-alcoholic cirrhosis [7, 8] and obesity [9, 10]. MetS is a common comorbidity of IBD, and their co-occurrence is increasing in incidence. MetS and IBD have several similar pathophysiological features, including immune imbalance, chronic inflammation, adipose tissue dysfunction, and disorders of the gut microbiota [11]. Although studies have suggested an association between MetS and a poor prognosis of IBD [12, 13], previous studies on the relationship between IBD and MetS have largely been limited to observational or single-center studies with small sample sizes. Consequently, the causal relationship between IBD and MetS remains unclear [14].

Mendelian randomization (MR) is a genetics-based research method used to assess the causal effects of exposure factors on outcomes. It employs genetic variations associated with these factors as instrumental variables. The core concept of this method is that genetic variation in the population is randomly distributed, similar to the randomization employed in randomized controlled trials; this effectively controls the influence of confounding factors [15].

Therefore, this study aimed to use MR to explore the causal relationship between MetS and IBD based on the latest summary statistics of genome-wide association studies (GWASs), providing new insights into the prevention and treatment of IBD.

Material and methods

The overall study design of this bidirectional two-sample MR analysis is shown in Figure 1. To be used as instrumental variables, single nucleotide polymorphisms (SNPs) were required to meet three assumptions: (1) they are associated with the exposure, (2) they are independent of any confound-

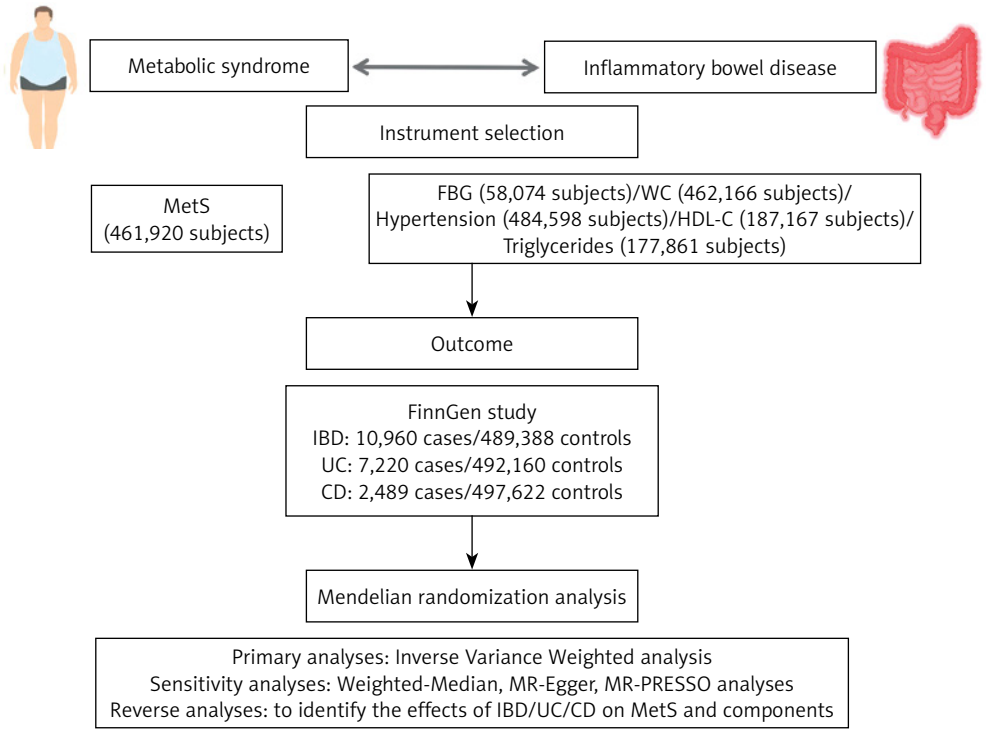

Figure 1. Overall design of the present Mendelian randomization analysis

Table I. Characteristics of the genome-wide association studies used in this analysis

Phenotypes	Ancestry	Sample size	Data sources
MetS	European	461,920	van Walree *et al.*
FBG	European	58,074	https://gwas.mrcieu.ac.uk/datas ets/ebi-a-GCST005186/
WC	European	462,166	https://gwas.mrcieu.ac.uk/datas ets/ukb-b-9405/
Hypertension	European	484,598	https://gwas.mrcieu.ac.uk/datas ets/ebi-a-GCST90038604/
HDL-C	Mixed (96% European)	187,167	https://gwas.mrcieu.ac.uk/datas ets/ieu-a-299/
Triglycerides	Mixed (96% European)	177,861	https://gwas.mrcieu.ac.uk/datas ets/ieu-a-302/
IBD	European	500,348	FinnGen consortium
UC	European	499,380	FinnGen consortium
CD	European	500,111	FinnGen consortium

ing factors in the exposure–outcome relationship, and (3) they affect the outcome solely through the exposure [16]. The detailed summary data used in the present study are shown in Table I. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization reporting guidelines [17]. All data used in this study are derived from published public databases; therefore, no additional ethical approval was required.

Source of GWAS data

MetS GWAS

GWAS data for MetS were obtained from the Center for Neurogenomics and Cognitive Research database, including data from a study by Van Walree *et al.* [18] – the largest GWAS study so far to focus on MetS, which includes data from 461,920 individuals of European ancestry. The GWAS summary data of the five components of MetS (waist circumference (WC), high blood pressure, fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) were obtained from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/).

IBD GWAS

GWAS data for IBD and its subtypes – UC and CD – were obtained from the latest FinnGen R12 dataset [19], which includes 10,960 cases and 489,388 controls for IBD, 7,220 cases and 492,160 controls for UC, and 2,489 cases and 497,622 controls for CD.

Instrument selection

Strict selection criteria and linkage disequilibrium clumping were used to identify suitable instrumental variables for the MR analyses. SNPs with a genome-wide significance level of $p < 5 \times 10^{-8}$ were included. Furthermore, we performed a linkage disequilibrium clumping and excluded SNPs with an r^2 value of ≥ 0.001 and a clump distance of ≤ 10,000 kb to eliminate SNPs that correlated more strongly with outcomes than with exposure [20]. The F statistic was calculated separately for each SNP. Weak instrumental variables were defined as those with an *F* statistic of < 10, and all weak instrumental variables were excluded from the analyses [21].

Statistical analysis

A generalized inverse variance weighted (IVW) MR approach was used for the principal analysis. MR analysis was conducted for each of the three European databases, and the overall effect of each specific outcome was assessed using a meta-analysis. Cochrane's Q was used to calculate the I^2 statistics to assess the heterogeneity of the SNP estimates. A random effects model was used when significant heterogeneity was detected ($p < 0.05$); otherwise, a fixed effects model was used. Several complementary methods were applied to provide reliable and consistent causal estimates, including the weighted median [22], MR-Egger [23], and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) [24] methods. The *p*-value of the MR-Egger method intercept was used to evaluate the horizontal pleiotropy, with $p < 0.05$ indicating the presence of horizontal pleiotropy. An MR-PRESSO analysis was performed to identify and eliminate outliers, and to evaluate whether a significant difference in the causal effect could be observed after these outliers were removed ($p < 0.05$). The leave-one-out method was used to determine whether the overall causal effect was influenced by any single SNP, which could potentially introduce bias. Multiple tests were performed using the Benjamini–Hochberg correction to control the false discovery rate; correlations with $p < 0.05$ were considered significant.

All statistical analyses were performed using the R packages MR-PRESSO and TwoSampleMR within the open-source statistical software R (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Causal role of MetS in IBD, UC, and CD

Our results suggested that MetS could increase the risk of CD (OR = 1.34, 95% CI: 1.009–1.779; $p = 0.043$) with low heterogeneity. Genetically predicted MetS was also not associated with IBD and UC (Figure 2). In further analysis, we found a causal relationship between waist circumference and CD (OR = 1.33, 95% CI: 1.05–1.684; $p = 0.018$) and a causal relationship between hypertension and UC (OR = 1.61, 95% CI: 1.084–2.39; $p = 0.018$) in the MetS component with low heterogeneity (Figure 2). Our study found no causal relationship between genetically predicted FBG, HDL-C, triglycerides and IBD, UC, and CD. The scatter plots for the forward analyses and the leave-one-out analyses for each SNP association are summarized in Supplementary Figures S1 and S2, respectively. Detailed information regarding the instrumental variables for MetS and components is provided in Supplementary Tables. Sensitivity analyses, including the weighted median, MR-Egger, and MR-PRESSO methods, yielded consistent findings (Table II). The statistical results between FBG and UC based on the MR-Egger intercept show horizontal pleiotropy, while other statistical results do not show horizontal pleiotropy (Table II).

Causal role of IBD, UC, and CD in MetS

In reverse analysis, our findings showed that genetically predicted IBD, UC, and CD were not associated with MetS (Figure 3). In addition, we found a causal relationship between IBD and triglycerides (OR = 1.019, 95% CI: 1.000–1.038; $p = 0.049$) with no heterogeneity (Figure 3). Our results suggest no causal relationship between genetically predicted IBD, UC, and CD and FBG, WC, HDL-C, and hypertension. No horizontal pleiotropy was observed for all outcomes. The sensitivity analysis revealed similar findings (Table III). Scatter plots for the reverse analyses and the plots of the leave-one-out analyses for each SNP are summarized in Supplementary Figures S3 and S4, respectively. Detailed information regarding the instrumental variables for IBD, UC, and CD is provided in Supplementary Tables.

Discussion

This is the first study to comprehensively examine the causal relationship between MetS and IBD, including the IBD subtypes UC and CD. After rigorous reverse variance weighted analysis and sensitivity analysis, our results revealed a significant association between MetS, WC, hypertension, triglycerides, and IBD.

The comorbidities of IBD must be considered during treatment, as they can alter disease activity and parenteral manifestations, ultimately affecting the disease prognosis and drug treatment responses. The global incidences of MetS and IBD have increased in tandem, and approximately 19.4% of patients with IBD also have MetS [25]. As a comorbidity of IBD, MetS increases the risk of cardiovascular disease, liver disease, and surgical complications and reduces patients' quality of life [5, 12, 25–27]. Obesity, a characteristic of MetS, may increase the incidence and severity of CD and the risk of cancer, and affect the patient's response to treatment, although MetS does not have the same impact in patients with UC [9, 28–30]. Previous studies on the effects of MetS on IBD were observational, rendering them susceptible to reverse causality and other biases. The causal relationship between MetS and IBD remains unclear, as some studies have reported conflicting results [31, 32]. Through the use of different estimation models and rigorous sensitivity analyses, MR effectively reduces potential biases such as confounding and reverse causality, enhancing the causal reasoning and ensuring the reliability and robustness of the study findings. The results of this study suggest that MetS may increase the risk of CD. In a further analysis of MetS components, increased WC appeared to have a more significant effect on risk of CD. In addition, we observed that hypertension may increase the risk of UC, and IBD may lead to elevated triglyceride levels.

Although there is limited research on the causal relationship between MetS and IBD, there have been several studies exploring whether obesity, a core component of MetS, has an impact on the development of IBD, but they have provided inconsistent and conflicting evidence [33–40]. While most cohort studies have proposed that general obesity, as represented by body mass index, increases the risk of CD and decreases the risk of UC [35, 38–40], a few studies have shown inconsistent findings [35, 37, 39]. As for abdominal obesity as measured by WC, limited cohort study evidence suggests a positive association with the risk of CD [34, 40]. WC usually reflects abdominal adipose tissue, including visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). VAT, adipocyte dysfunction, chronic low-grade inflammation, and insulin resistance are components of MetS [41], and VAT plays a central role in the pathophysiology of MetS. Therefore, VAT may contribute to chronic systemic inflammation in patients with

Exposures_Outcome	Used_SNPS	OR (95% CI)	*P*-value
Metabolic syndrome on IBD			
Inverse variance weighted	184	1.023 (0.861–1.216)	0.793
Weighted median	184	1.070 (0.852–1.343)	0.562
ME Egger	184	0.885 (0.549–1.426)	0.616
FBG on IBD			
Inverse variance weighted	20	0.869 (0.715–1.056)	0.158
Weighted median	20	0.990 (0.769–1.275)	0.937
ME Egger	20	0.990 (0.769–1.275)	0.551
WC on IBD			
Inverse variance weighted	363	1.058 (0.938–1.195)	0.358
Weighted median	363	1.025 (0.861–1.220)	0.784
ME Egger	363	1.064 (0.752–1.507)	0.725
Hypertension on IBD			
Inverse variance weighted	236	1.350 (0.971–1.878)	0.075
Weighted median	236	2.005 (1.309–3.071)	0.001
ME Egger	236	1.905 (0.805–4.508)	0.144
HDL-C on IBD			
Inverse variance weighted	82	1.029 (0.925–1.145)	0.600
Weighted median	82	0.988 (0.871–1.122)	0.854
ME Egger	82	1.016 (0.834–1.238)	0.873
Triglycerides on IBD			
Inverse variance weighted	50	0.980 (0.870–1.103)	0.736
Weighted median	50	0.933 (0.808–1.077)	0.344
ME Egger	50	0.896 (0.744–1.079)	0.252
Metabolic syndrome on UC			
Inverse variance weighted	185	0.944 (0.762–1.169)	0.596
Weighted median	185	0.939 (0.700–1.261)	0.676
ME Egger	185	0.788 (0.436–1.426)	0.432
FBG on UC			
Inverse variance weighted	21	0.825 (0.656–1.037)	0.099
Weighted median	21	0.926 (0.658–1.303)	0.659
ME Egger	21	1.280 (0.805–2.034)	0.310
WC on UC			
Inverse variance weighted	365	1.015 (0.876–1.176)	0.845
Weighted median	365	0.946 (0.752–1.191)	0.637
ME Egger	365	0.902 (0.591–1.378)	0.634
Hypertension on UC			
Inverse variance weighted	240	1.610 (1.084–2.390)	0.018
Weighted median	240	2.211 (1.326–3.686)	0.002
ME Egger	240	3.498 (1.245–9.828)	0.018
HDL-C on UC			
Inverse variance weighted	82	1.017 (0.897–1.154)	0.788
Weighted median	82	0.985 (0.827–1.174)	0.869
ME Egger	82	1.013 (0.801–1.282)	0.911
Triglycerides on UC			
Inverse variance weighted	50	0.999 (0.880–1.135)	0.993
Weighted median	50	0.909 (0.763–1.083)	0.285
ME Egger	50	0.933 (0.765–1.138)	0.497
Metabolic syndrome on CD			
Inverse variance weighted	190	1.340 (1.009–1.779)	0.043
Weighted median	190	1.336 (0.887–2.014)	0.166
ME Egger	190	1.594 (0.726–3.501)	0.247
FBG on CD			
Inverse variance weighted	21	0.767 (0.489–1.205)	0.250
Weighted median	21	0.995 (0.569–1.740)	0.985
ME Egger	21	1.012 (0.401–2.553)	0.980
WC on CD			
Inverse variance weighted	369	1.330 (1.050–1.684)	0.018
Weighted median	369	1.389 (0.971–1.987)	0.072
ME Egger	369	1.834 (0.930–3.617)	0.081
Hypertension on CD			
Inverse variance weighted	242	1.000 (0.553–1.810)	0.999
Weighted median	242	0.780 (0.340–1.789)	0.557
ME Egger	242	0.656 (0.138–3.114)	0.596
HDL-C on CD			
Inverse variance weighted	88	0.835 (0.696–1.001)	0.052
Weighted median	88	0.905 (0.706–1.161)	0.434
ME Egger	88	0.716 (0.511–1.004)	0.056
Triglycerides on CD			
Inverse variance weighted	53	1.098 (0.880–1.371)	0.407
Weighted median	53	1.056 (0.795–1.403)	0.707
ME Egger	53	1.105 (0.771–1.584)	0.590

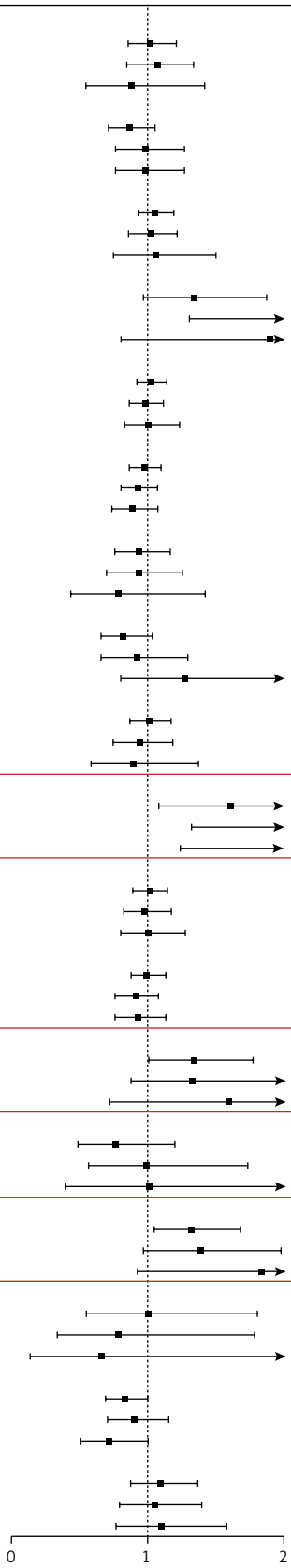

Figure 2. Genetically predicted association between MetS and IBD by forward MR analysis

IBD – inflammatory bowel disease, UC – ulcerative colitis, CD – Crohn's disease, FBG – fasting blood glucose, WC – waist circumference.

Table II. Results of the forward Mendelian randomization analysis for the effect of metabolic syndrome on inflammatory bowel disease

Exposure	Outcome	No. of SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	*P*-value	MR-Egger intercept (*P*-value)	Cochran's Q test (I^2)	*P*-value
MetS	IBD	184	IVW	1.023	0.861	1.216	0.793	0.522	348.189	< 0.001
			WM	1.070	0.852	1.343	0.562		(47.44%)	
			MR-Egger	0.885	0.549	1.426	0.616			
			MRPRESSO	1.023	1.010	1.037	0.793			
FBG	IBD	20	IVW	0.869	0.715	1.056	0.158	0.140	20.109	0.388
			WM	0.990	0.769	1.275	0.937		(5.51%)	
			MR-Egger	1.124	0.770	1.641	0.551			
			MRPRESSO	0.869	0.832	0.908	0.174			
WC	IBD	363	IVW	1.058	0.938	1.195	0.358	0.973	486.05	< 0.001
			WM	1.025	0.861	1.220	0.784		(25.52%)	
			MR-Egger	1.064	0.752	1.507	0.725			
			MRPRESSO	1.058	1.052	1.065	0.358			
Hypertension	IBD	236	IVW	1.350	0.971	1.878	0.075	0.397	383.977	< 0.001
			WM	2.005	1.309	3.071	0.001		(38.8%)	
			MR-Egger	1.905	0.805	4.508	0.144			
			MRPRESSO	1.350	1.321	1.379	0.076			
HDL-C	IBD	82	IVW	1.029	0.925	1.144	0.600	0.883	166.921	< 0.001
			WM	0.988	0.871	1.122	0.854		(51.47%)	
			MR-Egger	1.016	0.834	1.238	0.873			
			MRPRESSO	1.029	1.017	1.041	0.601			
Triglycerides	IBD	50	IVW	0.980	0.870	1.103	0.736	0.227	81.006	0.003
			WM	0.933	0.808	1.077	0.344		(39.51%)	
			MR-Egger	0.896	0.744	1.079	0.252			
			MRPRESSO	0.980	0.964	0.996	0.738			
MetS	UC	185	IVW	0.944	0.762	1.169	0.596	0.523	359.544	< 0.001
			WM	0.939	0.700	1.261	0.676		(48.82%)	
			MR-Egger	0.788	0.436	1.426	0.432			
			MRPRESSO	0.944	0.929	0.959	0.597			
FBG	UC	21	IVW	0.825	0.656	1.037	0.099	0.046	20.227	0.444
			WM	0.926	0.658	1.303	0.659		(1.12%)	
			MR-Egger	1.280	0.805	2.034	0.310			
			MRPRESSO	0.825	0.785	0.867	0.115			
WC	UC	365	IVW	1.015	0.876	1.176	0.845	0.562	483.305	< 0.001
			WM	0.946	0.752	1.191	0.637		(24.69%)	
			MR-Egger	0.902	0.591	1.378	0.634			
			MRPRESSO	1.015	1.007	1.023	0.845			
Hypertension	UC	240	IVW	1.610	1.084	2.390	0.018	0.112	374.894	< 0.001
			WM	2.211	1.326	3.686	0.002		(36.25%)	
			MR-Egger	3.498	1.245	9.828	0.018			
			MRPRESSO	1.610	1.569	1.651	0.019			
HDL-C	UC	82	IVW	1.017	0.897	1.154	0.788	0.970	152.668	< 0.001
			WM	0.985	0.827	1.174	0.869		(46.94%)	
			MR-Egger	1.013	0.801	1.282	0.911			
			MRPRESSO	1.017	1.003	1.032	0.788			
Triglycerides	UC	50	IVW	0.999	0.880	1.135	0.993	0.381	69.875	0.027
			WM	0.909	0.763	1.083	0.285		(29.88%)	
			MR-Egger	0.933	0.765	1.138	0.497			
			MRPRESSO	0.999	0.982	1.018	0.993			
MetS	CD	190	IVW	1.340	1.009	1.779	0.043	0.642	231.022	0.02
			WM	1.336	0.887	2.014	0.166		(18.19%)	
			MR-Egger	1.594	0.726	3.501	0.247			
			MRPRESSO	1.340	1.312	1.368	0.045			

Table II. Cont.

Exposure	Outcome	No. of SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	*P*-value	MR-Egger intercept (*P*-value)	Cochran's Q test (I^2)	*P*-value
FBG	CD	21	IVW	0.767	0.489	1.205	0.250	0.508	27.131	0.132
			WM	0.995	0.569	1.740	0.985		(26.28%)	
			MR-Egger	1.012	0.401	2.553	0.980			
			MRPRESSO	0.767	0.695	0.847	0.263			
WC	CD	369	IVW	1.330	1.050	1.684	0.018	0.323	443.917	0.004
			WM	1.389	0.971	1.987	0.072		(17.1%)	
			MR-Egger	1.834	0.930	3.617	0.081			
			MRPRESSO	1.330	1.313	1.346	0.018			
Hypertension	CD	242	IVW	1.000	0.553	1.810	0.999	0.566	304.114	0.004
			WM	0.780	0.340	1.789	0.557		(20.75%)	
			MR-Egger	0.656	0.138	3.114	0.596			
			MRPRESSO	1.000	0.963	1.039	0.999			
HDL-C	CD	88	IVW	0.835	0.696	1.001	0.052	0.294	126.869	0.003
			WM	0.905	0.706	1.161	0.434		(31.43%)	
			MR-Egger	0.716	0.511	1.004	0.056			
			MRPRESSO	0.835	0.819	0.851	0.055			
Triglycerides	CD	53	IVW	1.098	0.880	1.371	0.407	0.968	72.906	0.029
			WM	1.056	0.795	1.403	0.707		(28.68%)	
			MR-Egger	1.105	0.771	1.584	0.590			
			MRPRESSO	1.098	1.065	1.132	0.411			

MetS – metabolic syndrome, FBG – fasting blood glucose, WC – waist circumference, HDL-C – high-density lipoprotein cholesterol, IBD – inflammatory bowel disease, UC – ulcerative colitis, CD – Crohn's disease.

MetS or IBD [11]. As an important endocrine organ regulating the body's energy homeostasis, adipose tissue plays a key metabolic role by secreting adipokines with pro-inflammatory and anti-inflammatory activities [42]. In a normal metabolic state, the balance between pro-inflammatory and anti-inflammatory adipokines maintains homeostasis; however, excessive calorie intake can cause fat cells to become hypertrophic, leading to central obesity. If this state persists and exceeds the buffering capacity of adipocytes, the cells are subjected to oxidative stress, resulting in cellular disruption and the production by adipose tissue of abnormal levels of resistin, leptin, and adiponectin [43, 44]. Hypertrophic adipocytes secrete interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein-1, which recruit monocytes and promote their differentiation into pro-inflammatory macrophages. These macrophages infiltrate the VAT and promote chronic, low-grade inflammation throughout the body [45]. Unlike subcutaneous adipose tissue, VAT actively promotes local systemic inflammation [46]. Individuals with obesity and VAT are more likely to develop MetS and IBD than individuals with SAT [47]. In patients with CD, VAT will cover the intestinal surface to form "creeping fat". Creeping fat cells have inflammatory characteristics, and the expression of cytokines and adipokines involved in inflammation is increased [48]. As an important indicator of disease activity, creeping fat is found in 100% of patients with CD, whereas it is generally absent in UC [49]. In addition, compared with UC patients, the visceral adipose tissue of CD patients is more prone to inflammation and colonization by intestinal bacteria [50]. Therefore, MetS and WC may be more strongly associated with the risk of CD than UC.

Hypertension is an important component of MetS, and hypertension and IBD share some common core pathways in pathogenesis. Pro-inflammatory signaling molecules, including interleukin-1β, tumor necrosis factor-α, and interleukin-6, are significantly elevated in both diseases. These molecules coordinate chronic inflammation, endothelial dysfunction, and smooth muscle cell proliferation, which leads to plaque formation and vascular damage. In essence, the persistence of systemic inflammation triggered by these cytokines is the common driving force behind the development and progression of IBD and cardiovascular disease. The endothelium is an important regulator of vascular function and plays a key role in maintaining cardiovascular health. In healthy conditions, endothelium promotes vasodilation, inhibits thrombosis, and regulates inflammation. Endothelial dysfunction disrupts this delicate balance, resulting in impaired vasoconstriction and vasodilation [51]. A previous cohort study suggested that UC patients have a higher cumulative risk of developing hypertension than the general population [52]. Another meta-analysis found that

Exposures_Outcome	Used_SNPS	OR (95% CI)	*P*-value
IBD on Metabolic syndrome			
Inverse variance weighted	21	1.007 (0.998–1.016)	0.141
Weighted median	21	1.008 (0.995–1.021)	0.249
ME Egger	21	0.986 (0.956–1.016)	0.362
IBD on FBG			
Inverse variance weighted	25	0.994 (0.980–1.009)	0.450
Weighted median	25	0.984 (0.964–1.004)	0.125
ME Egger	25	0.972 (0.924–1.024)	0.298
IBD on WC			
Inverse variance weighted	53	1.004 (0.998–1.009)	0.190
Weighted median	53	1.006 (0.999–1.013)	0.703
ME Egger	53	0.999 (0.986–1.014)	0.938
IBD on Hypertension			
Inverse variance weighted	63	1.001 (0.999–1.004)	0.271
Weighted median	63	1.001 (0.998–1.005)	0.400
ME Egger	63	1.001 (0.995–1.007)	0.777
IBD on HDL-C			
Inverse variance weighted	22	0.995 (0.972–1.018)	0.644
Weighted median	22	0.995 (0.967–1.025)	0.751
ME Egger	22	1.002 (0.930–1.079)	0.960
IBD on Triglycerides			
Inverse variance weighted	23	1.019 (1.000–1.038)	0.049
Weighted median	23	1.009 (0.983–1.035)	0.511
ME Egger	23	0.988 (0.932–1.048)	0.699
UC on Metabolic syndrome			
Inverse variance weighted	14	0.996 (0.987–1.006)	0.457
Weighted median	14	1.004 (0.992–1.017)	0.495
ME Egger	14	1.003 (0.968–1.039)	0.861
UC on FBG			
Inverse variance weighted	19	1.002 (0.989–1.016)	0.726
Weighted median	19	0.988 (0.970–1.006)	0.206
ME Egger	19	0.957 (0.913–1.002)	0.077
UC on WC			
Inverse variance weighted	38	1.003 (0.997–1.010)	0.279
Weighted median	38	1.006 (0.999–1.013)	0.070
ME Egger	38	1.007 (0.989–1.025)	0.468
UC on Hypertension			
Inverse variance weighted	48	1.001 (0.998–1.003)	0.535
Weighted median	48	1.000 (0.997–1.003)	0.842
ME Egger	48	1.004 (0.996–1.011)	0.352
UC on HDL-C			
Inverse variance weighted	15	1.000 (0.980–1.021)	0.966
Weighted median	15	0.997 (0.973–1.021)	0.803
ME Egger	15	1.003 (0.930–1.082)	0.942
UC on Triglycerides			
Inverse variance weighted	17	1.011 (0.995–1.028)	0.173
Weighted median	17	1.005 (0.983–1.027)	0.667
ME Egger	17	1.016 (0.962–1.072)	0.581
CD on Metabolic syndrome			
Inverse variance weighted	5	0.997 (0.987–1.007)	0.560
Weighted median	5	0.997 (0.983–1.011)	0.648
ME Egger	5	1.031 (0.960–1.107)	0.466
CD on FBG			
Inverse variance weighted	5	1.008 (0.989–1.027)	0.414
Weighted median	5	1.012 (0.991–1.033)	0.251
ME Egger	5	0.998 (0.884–1.127)	0.978
CD on WC			
Inverse variance weighted	8	1.002 (0.996–1.008)	0.514
Weighted median	8	1.004 (0.997–1.012)	0.254
ME Egger	8	1.006 (0.989–1.023)	0.533
CD on Hypertension			
Inverse variance weighted	9	1.003 (1.000–1.006)	0.085
Weighted median	9	1.003 (0.999–1.007)	0.203
ME Egger	9	1.002 (0.994–1.011)	0.574
CD on HDL-C			
Inverse variance weighted	7	0.991 (0.966–1.018)	0.520
Weighted median	7	0.995 (0.969–1.022)	0.705
ME Egger	7	1.072 (0.916–1.254)	0.425
CD on Triglycerides			
Inverse variance weighted	7	1.149 (0.931–1.417)	0.196
Weighted median	7	1.025 (0.997–1.055)	0.081
ME Egger	7	0.464 (0.151–1.425)	0.237

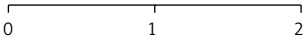

Figure 3. Genetically predicted association between IBD and MetS by reverse MR analysis

IBD – inflammatory bowel disease, UC – ulcerative colitis, CD – Crohn's disease, FBG – fasting blood glucose, WC – waist circumference.

Table III. Results of the reverse Mendelian randomization analysis for the effect of inflammatory bowel disease on metabolic syndrome

Exposure	Outcome	No. of SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	*P*-value	MR-Egger intercept (*P*-value)	Cochran's Q test (I^2)	*P*-value
IBD	MetS	21	IVW	1.007	0.998	1.016	0.141	0.164	23.041	0.287
			WM	1.008	0.995	1.021	0.249		(13.2%)	
			MR-Egger	0.986	0.956	1.016	0.362			
			MRPRESSO	1.007	1.005	1.009	0.157			
IBD	FBG	25	IVW	0.994	0.980	1.009	0.450	0.385	30.476	0.169
			WM	0.984	0.964	1.004	0.125		(21.25%)	
			MR-Egger	0.972	0.924	1.024	0.298			
			MRPRESSO	0.994	0.991	0.997	0.458			
IBD	WC	53	IVW	1.004	0.998	1.009	0.190	0.533	72.895	0.029
			WM	1.006	0.999	1.013	0.073		(28.67%)	
			MR-Egger	0.999	0.986	1.014	0.938			
			MRPRESSO	1004	1.003	1.004	0.196			
IBD	Hypertension	63	IVW	1.001	0.999	1.004	0.427	0.876	83.587	0.035
			WM	1.001	0.998	1.005	0.400		(25.83%)	
			MR-Egger	1.000	0.995	1.007	0.777			
			MRPRESSO	1.001	1.001	1.002	0.275			
IBD	HDL-C	22	IVW	0.995	0.972	1.018	0.644	0.840	32.505	0.052
			WM	0.995	0.967	1.025	0.751		(35.39%)	
			MR-Egger	1.002	0.930	1.079	0.960			
			MRPRESSO	0.995	0.990	0.999	0.649			
IBD	Triglycerides	23	IVW	1.019	1.000	1.038	0.049	0.294	24.074	0.343
			WM	1.009	0.983	1.035	0.511		(8.61%)	
			MR-Egger	0.988	0.932	1.048	0.699			
			MRPRESSO	1.019	1.015	1.023	0.062			
UC	MetS	14	IVW	0.996	0.987	1.006	0.457	0.696	15.195	0.295
			WM	1.004	0.992	1.017	0.495		(19.97%)	
			MR-Egger	1.003	0.968	1.039	0.861			
			MRPRESSO	0.996	0.994	0.999	0.470			
UC	FBG	19	IVW	1.002	0.989	1.016	0.726	0.054	20.707	0.294
			WM	0.988	0.970	1.006	0.206		(13.07%)	
			MR-Egger	0.957	0.913	1.002	0.077			
			MRPRESSO	1.002	0.999	1.006	0.730			
UC	WC	38	IVW	1.003	0.997	1.010	0.279	0.704	72.739	< 0.001
			WM	1.006	0.999	1.013	0.070		(49.13%)	
			MR-Egger	1.007	0.989	1.025	0.468			
			MRPRESSO	1.003	1.002	1.004	0.286			
UC	Hypertension	42	IVW	1.000	0.998	1.003	0.545	0.443	90.352	< 0.001
			WM	1.000	0.997	1.003	0.842		(47.98%)	
			MR-Egger	1.004	0.996	1.011	0.352			
			MRPRESSO	1.000	1.000	1.001	0.538			
UC	HDL-C	15	IVW	1.000	0.980	1.021	0.966	0.949	19.628	0.142
			WM	0.997	0.973	1.021	0.803		(28.67%)	
			MR-Egger	1.003	0.930	1.082	0.942			
			MRPRESSO	1.000	0.995	1.006	0.966			
UC	Triglycerides	17	IVW	1.011	0.995	1.028	0.173	0.877	11.301	0.791
			WM	1.005	0.983	1.027	0.667		(41.58%)	
			MR-Egger	1.016	0.962	1.072	0.581			
			MRPRESSO	1.011	1.008	1.015	0.124			
CD	MetS	5	IVW	0.997	0.987	1.007	0.560	0.423	3.516	0.475
			WM	0.997	0.983	1.011	0.648		(13.77%)	
			MR-Egger	1.031	0.960	1.107	0.466			
			MRPRESSO	0.997	0.993	1.001	0.568			

Table III. Cont.

Exposure	Outcome	No. of SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	*P*-value	MR-Egger intercept (*P*-value)	Cochran's Q test (I^2)	*P*-value
CD	FBG	5	IVW	1.008	0.989	1.027	0.414	0.883	6.291	0.178
			WM	1.012	0.991	1.033	0.251		(36.42%)	
			MR-Egger	0.998	0.884	1.127	0.978			
			MRPRESSO	1.008	0.999	1.016	0.460			
CD	WC	8	IVW	1.002	0.996	1.008	0.514	0.661	2.252	0.944
			WM	1.004	0.997	1.012	0.254		(210.87%)	
			MR-Egger	1.006	0.989	1.023	0.533			
			MRPRESSO	1.002	1.000	1.003	0.288			
CD	Hypertension	48	IVW	1.001	0.998	1.003	0.535	0.443	90.352	< 0.001
			WM	1.000	0.997	1.003	0.842		(47.98%)	
			MR-Egger	1.004	0.996	1.011	0.352			
			MRPRESSO	1.000	1.000	1.001	0.538			
CD	HDL-C	7	IVW	0.991	0.966	1.018	0.520	0.368	12.371	0.054
			WM	0.995	0.969	1.022	0.705		(51.5%)	
			MR-Egger	1.072	0.916	1.254	0.425			
			MRPRESSO	0.991	0.982	1.001	0.544			
CD	Triglycerides	7	IVW	1.149	0.931	1.417	0.196	0.169	838.822	< 0.001
			WM	1.025	0.997	1.055	0.081		(99.28%)	
			MR-Egger	0.464	0.151	1.425	0.237			
			MRPRESSO	1.149	1.061	1.244	0.243			

MetS – metabolic syndrome, FBG – fasting blood glucose, WC – waist circumference, HDL-C – high-density lipoprotein cholesterol, IBD – inflammatory bowel disease, UC – ulcerative colitis, CD – Crohn's disease.

patients with IBD had a higher risk of co-existing hypertension [53]. However, the evidence for a causal relationship between hypertension and IBD remains limited. This study found for the first time that hypertension may increase the risk of UC through MR analysis, but its mechanism still needs further study. In addition, previous studies have shown elevated triglyceride levels in IBD patients [54, 55], and triglycerides play an important role in atherosclerosis [56]; similarly, the results of this study indicate that IBD increases triglyceride levels, suggesting that IBD may increase the risk of cardiovascular disease.

Although this study used MR to effectively control for confounding factors and inverse causality, some limitations remain. First, MR analyses infer causal hypotheses by randomly assigning genetic variants, so it is difficult to fully distinguish between pleiotropy and mediations during the analysis. Second, the genetic data used in this study were primarily derived from European populations and may limit the applicability of the findings to other ethnicities and regions. Finally, larger sample sizes and more advanced methodologies are needed to confirm these findings and enhance the statistical power.

In conclusion, this MR analysis showed a causal relationship between genetically predicted MetS and CD, and genetically predicted hypertension and UC. Therefore, these patients need to be closely monitored clinically for the risk of CD/UC comorbidities. In patients with IBD, close monitoring of triglyceride-associated cardiovascular risk is required.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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